PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/002637	12.03.2004	18.03.2003

International Patent Classification (IPC) or both national classification and IPC
A61K35/78, A61K31/14, C07D221/18, C07D491/22, C07F9/564, C07F9/6561, C07F9/59, C07F9/6533,

Applicant
NOWICKY, Wassyl

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/002637

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-3, 5-8, 11-25 (all partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-3, 5-8, 11-25 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. which have been searched (cf. point III above)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	24,25
	No:	Claims	1-23
Inventive step (IS)	Yes:	Claims	24,25
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-25
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/002637

The application relates to alkaloid reaction products comprising a quaternary nitrogen. The alkaloid starting material contained a tertiary nitrogen atom which was made quaternary by reaction of the alkaloid with an alkylating agent. The group making the alkaloid quaternary is H, methyl, ethyl or a tris(1-aziridinyl)phosphine sulphide residue. Also claimed are particular chelidonine derivatives, the process for preparing the alkaloid reaction products and the use of the reaction products in the manufacture of pharmaceutical compositions for the treatment or prophylaxis of a number of medical conditions.

Re Item III.

As already indicated in the search report, the search was limited to the reaction products of the particular alkaloids given in claim 4 and the chelidonine derivatives of claim 9. Therefore this opinion is to be only regarded as complete for the subject-matter of claims 4, 9 and 10 and claims dependent thereon as these were the only claims searched in their entirety.

Re Item IV.

With a number of compounds being already known in the art, unity is not considered present between the methods for preparing the compounds and the use of the compounds for preparing medicaments.

Re Item V.

The prior art documents listed in the search report will be referred to as follows:

D1: DATABASE CHEMICAL ABSTRACTS [Online] Database accession no. 1982:173909 XP002239900 & ZHAO Y ET AL: 'Studies on the antimalarial activity of protopine derivatives' CHINESE PHARMACEUTICAL BULLETIN (YAOXUE TONGBAO), vol. 16, no. 6, June 1981 (1981-06), pages 7-10, XP001147793 ISSN: 0512-7343

D2: TANAKA S ET AL: 'Influence of natural and synthetic compounds on cell surface expression of cell adhesion molecules, ICAM-1 and VCAM-1' PLANTA MEDICA, THIEME, STUTTGART, DE, vol. 67, no. 2, 2001, pages 108-113, XP009003131 ISSN: 0032-0943

D3: SCHMELLER T ET AL: 'Biochemical activities of berberine, palmatine and sanguinarine mediating chemical defence against microorganisms and herbivores' PHYTOCHEMISTRY, PERGAMON PRESS, GB, vol. 44, no. 2, January 1997 (1997-01), pages 257-266, XP004292781 ISSN: 0031-9422

D4: SCHLOTTERBECK J O ET AL: 'Beiträge zur Chemie des stylophorum diphyllum' CHEMISCHE BERICHTE, vol. 35, 1902, pages 7-23, XP009009873 ISSN: 0009-2940

D5: HENSCHKE A: 'I. Über das Chelidonin' ARCHIV DER PHARMACIE, vol. 226, 1888, pages 624-644, XP009009872 ISSN: 0365-6233

D6: WALZTEROVÁ D ET AL: 'Inhibition of liver alanine aminotransferase activity by some benzophenanthridine alkaloids' JOURNAL OF MEDICINAL CHEMISTRY, vol. 24, no. 9, September 1981 (1981-09), pages 1100-1103, XP002239893 ISSN: 0022-2623

D7: ISHII H ET AL: 'Studies on the chemical constituents of rutaceous plants. LX. Development of a versatile method for syntheses of the antitumour benzo[c]phenanthridine alkaloids. 9. Efficient syntheses and antitumour activities of nitidine and related non-phenolic benzo[c]phenanthridine alkaloids' CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 33, no. 10, 1985, pages 4139-4151, XP001147415 ISSN: 0009-2363

D8: LOMBARDINI J B ET AL: 'Effects of benzophenanthridine alkaloids on the phosphorylation of an approx 44 kDa protein present in a mitochondrial fraction of the rat heart' BIOCHEMICAL PHARMACOLOGY, vol. 51, no. 2, 26 January 1996 (1996-01-26), pages 151-157, XP002239894 ISSN: 0006-2952

D9: NAKANISHI T ET AL: 'Structural considerations of NK109, an antitumour benzo[c]phenanthridine alkaloid' JOURNAL OF NATURAL PRODUCTS, vol. 62, no. 6, June 1999 (1999-06), pages 864-867, XP002239895 ISSN: 0163-3864

D10: VALPUESTA M ET AL: 'From protopines to berbines: synthesis of 1-methoxystylopine and its N-metho salts from coulteropine' TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 58, no. 25, 17 June 2002 (2002-06-17), pages 5053-5059, XP004366428 ISSN: 0040-4020

D11: SLAVIK J ET AL: 'Quaternary alkaloids from the roots of Argemone platyceras LINK et OTTO' COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, vol. 41, 1976, pages 285-9, XP009009913 ISSN: 0010-0765

D12: SCHMIDT E: '46. Über Paveraceen-Alkaloïde' ARCHIV DER PHARMACIE, vol. 231, 1893, pages 168-183, XP009009914 ISSN: 0365-6233

D13: TAKAO N ET AL: 'Studien über die Alkaloide de Pavaveraceen. Die Alkaloide von Corydalis incisa. (10). Über die struktur des (+)-14-Epicorynolins' CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 21, 1973, pages 1096-1102, XP009009871 ISSN: 0009-2363

D14: DANCKWORTT P W : 'Zur Kenntnis des Protopins und Kryptopins' ARCHIV DER PHARMACIE, vol. 250, 1912, pages 590-646, XP009009915 ISSN: 0365-6233

D15: MANSKE R H F ET AL: 'The alkaloids of papaveraceous plants. XXXIV. Hunnemannia fumariaefolia Sweet and the constitution of a new alkaloid, hunnemanine' JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 64, no. 7, July 1942 (1942-07), pages 1659-1661, XP002239896 ISSN: 0002-7863

D16: REDEMANN C E ET AL: 'Characterisation of certain alkaloids from Fagara coco' JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 71, no. 3, 19 March 1949 (1949-03-19), pages 1030-1034, XP002239897 ISSN: 0002-7863

D17: ULRICHOVÁ J ET AL: 'Cytotoxicity of natural compounds in hepatocyte cell culture models. The case of quaternary benzo[c]phenanthridine alkaloids' TOXICOLOGY LETTERS, vol. 125, no. 1-3, 15 December 2001 (2001-12-15), pages 125-132, XP002239898 ISSN: 0378-4274

D18: ZHANG G-L ET AL: 'Alkaloids from Dactylicapnos torulosa' PHYTOCHEMISTRY, vol. 40, no. 1, 1995, pages 299-305, XP002239899 ISSN: 0031-9422

i. Sanguinarine

The applicant is asked to explain to the Examining Division why sanguinarine is included in the list of claim 4 as sanguinarine already contains a quaternary nitrogen atom with the nitrogen being bonded thought an imine link to a vicinal carbon atom. Sanguinarine would therefore not react with the alkylating agent. Sanguinarine and its salts are already known in the art to treat a number of ailments as is demonstrated in documents D2, D3, D6-D9, D17.

ii. Compound claims 9 and 10

The particular chelidonine derivatives claimed in claims 9 and 10 are not to be seen as new as documents D4 and D5 disclose compounds falling under their scope. D4 discloses the ethyl iodide, the hydrogen iodide and hydrogen chloride salts of chelidonine and D5 the ethyl iodide and ethyl chloride salts. Claims 9 and 10 therefore lack novelty. No medical use is associated with these compounds in D4 and D5.

iii. Excluding sanguinarine and similar imine-bond containing quaternary nitrogen containing alkaloids, some of the other alkaloids listed in claim 4 would appear to have already been alkylated to form compounds falling under the scope of claims 1-5.

In D1, the compound A2 (protopine methyl iodide) is disclosed.

D10 discloses the compounds 3a, 3b, 4a, 4b, 5a and 5b which are seen to fall under the presently-claimed scope.

D11 discloses stylopine methiodide and methperchlorate.

Methyliodide homochelidonine is disclosed on page 168 of D12.

Compound 4 from D13 is also considered to fall under the scope of the present application.

D14 gives a number of derivatives of protopine which are novelty-destroying (cf. pages 632-9.

Hunnemanine-O-ethyl ether disclosed in column 2 on page 1660 of D15 is considered to anticipate the alkaloid reaction products of the present application.

Fagarine (otherwise known as allocryptopine) derivatives falling under the presently-claimed scope are disclosed in D16.

N-methylstylopium chloride (6) is disclosed in D18.

iv. Medical use of quaternary nitrogen containing derivatives of the alkaloids of claim 4

excluding sanguinarine (claims 23-25):

There would appear to be only one anticipating document for the use of quaternary nitrogen derivatives used as medicines, this being in document D1 (Chinese) where M-methylprotopine chloride is tested on patients suffering from malaria. Claim 23 therefore lacks novelty.

v. Methods of preparation claims:

The claims directed to the method of preparation of the alkaloid derivatives would appear to be either already known in the art for known compounds or easily derivable from the methods known in the art.

vi.. Amendments to overcome the above objections?

Claims directed to the use of the reaction products of alkaloids of claim 4 containing a quaternary nitrogen (sanguinarine excluded) for the preparation of medicaments for treating the particular ailments given in claims 24 and 25 would, for example, be considered to meet the requirements of Articles 33(2) and (3) PCT.

Re Item VII.

To meet the requirements of Rule 5.1(a)(ii) PCT, a number of the documents mentioned in the search report should be identified in the description and the relevant background art disclosed therein should be briefly discussed (depending upon how the application is restricted to overcome the above objections).